#922

PHARMACOLOGY

Comm.
Dr. Bing
Dr. Gardner
Dr. Jacobson

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
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Application for Research Grant
(Use extra pages as needed)

Date: 7/11/73

1. Principal Investigator (give title and degrees):
Guenther Boden, M.D.
Assistant Professor of Medicine and Assistant Director of the General Clinical Research Center

2. Institution & address:

Temple University Health Sciences Center
3401 N. Broad Street
Philadelphia, Pennsylvania 19140

3. Department(s) where research will be done or collaboration provided:

Department of Medicine, Temple University Health Sciences Center

4. Short title of study:

Effect of Nicotine and Cigarette Smoke on Secretin Secretion

5. Proposed starting date: January 1, 1974

6. Estimated time to complete: 2 years

7. Brief description of specific research aims:

Specific Aims: Previously published data suggest that nicotine inhibits pancreatic secretion of water and bicarbonate (1,2). The specific aims of the proposed study are: 1) to determine whether nicotine or cigarette smoke do indeed inhibit pancreatic secretion of water and bicarbonate and 2) if so, to determine whether the inhibition is mediated by the gastrointestinal hormone secretin or by a direct effect on the pancreas or both. To do this we intend to study the acute effects of intravenously infused nicotine or inhaled cigarette smoke on basal as well as HCl stimulated serum secretin concentrations and on pancreatic volume and bicarbonate secretion in dogs.

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8. Brief statement of working hypothesis.

It is well established that more smokers than non-smokers suffer from duodenal ulcers. Furthermore there is delayed healing of peptic ulcers in smokers as compared to non-smokers (3). The reason for this, however, remains unclear. In order to cause or maintain duodenal ulcers nicotine probably would have to increase duodenal acidity. This could be effected 1) by increased gastric secretion of HCl or 2) by decreased neutralization of a normal amount of gastric acid in the duodenum. The first possibility seems unlikely, since gastric acid secretion in smokers has not been found to be increased by most investigators (4-8). The latter possibility, however, has been supported recently by findings of Jacobson and his group (1,2). They reported that nicotine acutely inhibited pancreatic secretion of fluid and bicarbonate, the major buffers for acid in the duodenum. On the basis of these findings, it appears likely, that insufficient neutralization of acidic duodenal contents may be an important factor for the formation or maintenance of duodenal ulcers in smokers.

The mechanism by which nicotine inhibits pancreatic secretion is not known. Jacobson (9) speculated that at least part of the action of nicotine might be mediated by inhibition of the release of secretin, the major stimulus for pancreatic secretion of water and bicarbonate. Until recently this possibility could not be directly investigated due to the lack of adequate assay methods for the measurement of secretin in blood. We have recently developed a sensitive, specific and reproducible radioimmunoassay

9. Details of experimental design and procedures (append extra pages as necessary) (continued on next page)

I. Operative Procedures: The studies will be performed on overnight fasted healthy normal mongrel dogs weighing between 15 and 25 kg. The animals will be anesthetized by I.V. injection of Nembutal (approximately 6 mg/kg). They will be intubated and artificially respirated. Laporotomy will be performed and polyethylene catheters will be inserted into both femoral veins and the portal vein, 1-2 inches distal from the portal area. Then, the minor pancreatic duct will be ligated and a small polyvinyl catheter will be inserted into the major pancreatic duct between the head of the pancreas and the duodenal wall. A double lumen tube will be inserted through a gastrostomy opening into the stomach, passed through the pylorus and its position will be stabilized 1-2 inches distal from the duodenal bulb.

II. Experimental Design:

A. Effect of nicotine or cigarette smoke on basal IRS secretion: Each group of experiments will include three test periods. After an initial control period (-15 minutes until 0 minutes) nicotine (12.5 - 50 mg/kg) will be infused for 30 minutes. This will be followed by another control period. In a separate group of experiments inhalation of cigarette smoke will replace the infusion of nicotine. To accomplish this, cigarettes will be taped to the end of the trachial tube.

B. Effect of nicotine or cigarette smoke on HCl stimulated IRS secretion: Each experiment will include four test periods. After a brief control period (-15 minutes until 0 minutes) HCl (160 mmol in distilled water) will be infused at a rate of 4 ml per minute for 30 minutes. Nicotine (12.5 to 50 µg/kg) will be infused I.V. together with HCl. This will be followed by a rest period (30-60 minutes and a second infusion of HCl (60-90 minutes). Again, in a separate group of experiments inhalation of cigarette smoke will replace the infusion of nicotine.

III. Laboratory Determinations:

A. Collection of blood. Preparation of serum: Blood samples will be obtained from portal and femoral veins at frequent intervals before, during and after nicotine and/or HCl infusion, allowed to clot and will be centrifuged at 4° C. Serum will be stored at -15° C until assayed.

B. Determination of immunoreactive secretin (IRS): IRS will be measured by a sensitive and specific radioimmunoassay which has recently been described in detail (10). (A reprint of this article is added).

C. Determination of pancreatic volume and bicarbonate: Volume of pancreatic fluid will be collected in 15 minute intervals. Bicarbonate concentrations will be measured by adding 0.5 ml of pancreatic fluid to 1.0 ml of 0.1 N HCl, bringing the mixture briefly to boil and back titrating the residual HCl with 0.1 N sodium hydroxide in an automatic titrator (pH 7.0). In addition, pH will be measured in samples of duodenal fluid collected at frequent intervals.

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8. Brief statement of working hypothesis (continued):

for secretin (10). This assay enables us to directly study the effects of nicotine or cigarette smoke on circulating levels of immunoreactive secretin under basal and HCl stimulated conditions.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Dogs will be housed in the animal facilities which are located on the ninth floor of the Research Building of Temple University Health Sciences Center. All dog experiments will be performed in the surgical research laboratory also located on the 9th floor of the same building. All laboratory determinations will be performed in the laboratory of the principal investigator which is located on the second floor of the hospital of the Temple University Health Sciences Center.

11. Additional facilities required:

None

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12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

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## REFERENCES


1. Konturek, S.J., Solomon, T., McCreight, W.G., Johnson, L.R. and Jacobson, E.D. Effects of nicotine on gastrointestinal secretions. Gastroenterology 60:1098-1105, 1971.

2. Bynum, T.E., Solomon, T.E., Johnson, L.R. and Jacobson, E.D. Inhibition of pancreatic secretion in man by cigarette smoking. GUT 13:361-365, 1972.

3. Doll, R., Jones, F.A. and Pygott, F. Effect of smoking on the production and maintenance of gastric and duodenal ulcers. Lancet 1:657-662, 1958.

4. Thompson, J.H. Effects of nicotine and tobacco smoke on gastric secretion in rats with gastric fistulas. Dig. Dis. 15:209-217, 1970.

5. Naitove, A., Constantian, M.B., Arkins, T. Gastric hemodynamic effects of smoking and nicotine. Gastroenterology 58:1058, 1970.

6. Wilkinson, A.R. and Johnson, D. Inhibitory effect of cigarette smoking on gastric secretion stimulated by pentagastrin in man. Lancet 2:628-632, 1971.

7. Debas, H.T., Cohen, M.M., Holubitsky, I.B. and Harrison, R.C. Effect of cigarette smoking on human gastric secretory responses. GUT 12:93-96, 1971.

8. Paper, D.W. and Raine, J.M. Effect of smoking on gastric secretion. Lancet 1:696-698, 1959.

9. Ulcer 'smoke ring' clarified. Medical World News, June 4, 1971. p. 23.

10. Boden, G. and Chey, W.Y. Preparation and specificity of antiserum to synthetic secretin and its use in a radioimmunoassay (RIA). Endocrinology 92:1617-1624, 1973.


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14. First year budget

| A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested) | % time | Amount | Fringe Benefits |
|---|---|---|---|
| Guenther Boden, M.D. | 25 | REDACTED | |
| Shreekan Murthy, Ph.D. | 100 | | |
| Technical | | | |
| To be recruited | 100 | REDACTED | |
| | Sub-Total for A | REDACTED | |
| B. Consumable supplies (by major categories) | | | |
| Glassware | | 500 | |
| Dogs | | 3,000 | |
| Supplies for animal surgery | | 1,000 | |
| Supplies for radioimmunoassay: | | | |
| Radioisotopes | | 1,500 | |
| Reagents and antisera | | 500 | |
| | Sub-Total for B | 6,500 | |
| C. Other expenses (itemize) | | | |
| Service contract for gamma counter | | 680 | |
| | Sub-Total for C | 680 | |
| | Running Total of A + B + C | REDACTED | |
| D Permanent equipment (itemize) | | | |
| Desk calculator | | 250 | |
| Centrifuge (International Model RN-S) | | 410 | |
| | Sub Total for D | 660 | |
| E Indirect costs (15% of A+B+C) | E | 4,636 | |
| | Total request | REDACTED | |

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15. Estimated future requirements:

| | Salaries | Consumable Suppl | Other Expenses | Permanent Equip. | Indirect Costs | Total |
|---|---|---|---|---|---|---|
| Year 2 | REDACTED | 6,500 | 680 | | 4,955 | REDACTED |
| Year 3 | | | | | | |

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16. Other sources of financial support

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

| Title of Project | Source (give grant numbers) | Amount | Inclusive Dates |
|---|---|---|---|
| Secretin secretion in normal subjects and in patients with diabetes mellitus | Grant in aide, Pfizer Pharmaceutical Co., N.Y. N.Y. | $15,000 | 2/73 - 2/74 |

PENDING OR PLANNED

| Title of Project | Source (give grant numbers) | Amount | Inclusive Dates |
|---|---|---|---|
| Influence of endogenous secretin on insulin regulation | AM 16348 01 PHS - NIH Pending | 39,491 | |

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Guenther Boden, M.D.

Signature G. Boden Date 7/9/73

Telephone 215 (Area Code) 221 (Number) 3089 (Extension)

Checks payable to

Temple University Health Sciences Center

Mailing address for checks

Attn: Mr. David W. Siegel
Temple University Health Sciences Center
3400 N. Broad Street
Philadelphia, Pa. 19140

Responsible officer of institution

Typed Name Mr. David W. Siegel

Title Associate Vice President for Administration

Signature [signature] Date 7/11/73

Telephone 215 (Area Code) 221 (Number) 3246 (Extension)

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# CURRICULUM VITAE

Name: Guenther Boden, M.D.

Born: REDACTED

Marital Status: REDACTED

Children: REDACTED

MEDICAL TRAINING:

| Institution and Location | Degree | Year Conferred |
|---|---|---|
| Heidelberg University, School of Medicine | M.S. | 8/27/56 |
| Munich University, School of Medicine | M.D. | 12/5/59 |
| Intern - City Hospital and University Hospital, Hamburg and Berlin (Germany) | | 1/1/60-3/31/62 |
| Resident - City Hospital for Dermatology Stuttgart, Germany | | 4/1/62-12/31/62 |
| Assistant in Biochemistry - Tuebingen University, Dept. of Biochemistry, Tuebingen, Germany | | 1/1/63-4/30/65 |
| Research Fellow in Medicine - E.P. Joslin Research Laboratory, Boston, Mass. (Dept. of Medicine, Harvard Medical School) | | 5/1/65-9/30/67 |
| Assistant in Medicine - Peter Bent Brigham Hospital, Boston, Mass. | | 7/1/65-6/30/66 |
| Assistant Resident in Medicine - Rochester General Hospital, Rochester, New York | | 10/1/67-9/30/68 |
| Associate Resident in Medicine - Rochester General Hospital, Rochester, New York | | 10/1/68-2/28/70 |

APPOINTMENTS - MEDICAL SCHOOL:

Assistant Professor of Medicine and Assistant Director, General Clinical Research Center, Temple University Health Sciences Center, Temple University, Philadelphia, Pa. 3/1/70 -

Specialty Affiliations: REDACTED

Licensure: Pennsylvania REDACTED

Honors: Rochester, New York Regional Diabetes Award, 1970

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The following publications of the principal investigator are relevant to the proposed research:

1. Boden, G. and Chey, W.Y.: Preparation and specificity of antiserum to synthetic secretin and its use in a radioimmunoassay (RIA). Endocrinology 92:1617-1624, 1973.

2. Boden, G., Dinoso, V. and Owen, O.E.: Immunological comparison of natural and synthetic secretins. Horm. Metab. Res. 1973 (August).

3. Boden, G.: The secretin radioimmunoassay. Chapter 27 in "Methods of Hormone Radioimmunoassay. B.M. Jaffe and H. Behrman, eds. Academic Press. New York and London. 1974 (in press).

4. Gulati, S.C. and Boden, G.: Organ distribution and excretion of radioactivity after injection of $^{125}$I-secretin in rats. Presented at the Eastern Section AFCR, Boston, January, 1973. Clin. Res. 20:869, 1972.

5. Boden, G., Gulati, S.C. and Essa, H.: Influence of intraduodenal HCl on immunoreactive secretin (IRS) levels in dogs. Presented at the National Meeting AFCR, Atlantic City, April, 1973. Clin. Res. 21:508, 1973.

6. Boden, G. and Dinoso, V.P.: Immunoreactivities of natural and synthetic secretins. Presented at the 74th Annual Meeting of the American Gastroenterological Association, May 1973, New York, N.Y. Gastroenterology 64:878, 1973.

7. Boden, G., Gulati, S.C., Owen, O.E. and Shuman, C.R.: The insulinogenic effect of endogenous secretin. Presented at the 33rd Annual Meeting of the American Diabetes Association, Chicago, June, 1973. Diabetes 22: 304, 1973 (Suppl. 1).

8. Boden, G., Gulati, S.C., Essa, N. and Owen, O.E.: Influence of endogenous secretin on insulin secretion. To be presented at the 8th Congress of the International Diabetes Federation, Brussels, Belgium. July, 1973.

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1. Weitzel G, Schaeg W, Boden G, Willms B: Influence of photooxidation on histindincontent and activity of insulin (German), Liebigs Ann Chem 689:248-258, 1965.

2. Weitzel G, Schaeg W, Boden G, Willms B: Histindincontent and activity of insulin (German). Z.f. Naturforschung 20b, No. 5, 1965.

3. Boden G, Willms B: Influence of insulin on carbohydrate and lipid-metabolism of the perfused liver in normal and alloxan-diabetic rats, Klin Wschr 44:579-583, 1966 (German)

4. Boden G, Soeldner JS: A sensitive double antibody radioimmunoassay for human growth hormone (HGH) levels of serum HGH following rapid tolbutamide infusion. Diabetologia 3:413-421, 1967.

5. Boden G, Soeldner JS, Steinke J, Thorn GW: Serum human growth hormone (HGH) responses to IV glucose: Diagnosis of acromegaly in females and males. Metabolism 17:1-9, 1968.

6. Boden G, Soeldner JS, Gleason RE, Marble A: Elevated serum human growth hormone and decreased serum insulin in prediabetic males after intravenous tolbutamide and glucose. J Clin Invest 47:729-739, 1968.

7. Boden G, Soeldner JS, Gleason RE, Marble A: Early diabetes mellitus: Decreased serum insulin (IRI) and elevated serum growth hormone (HGH) in pre-diabetics. Diabetes. Edited by J Oestman. Excerpta Medica Foundation. Amsterdam. ICS 172 (Suppl.): 222-225, 1969.

8. Soeldner, JS, Soenksen PH, Gleason RE, Boden, G: The possible role of growth hormone in the pathogenesis of diabetes mellitus. The Actions of Hormones. Edited by P. P. Foa. CC Thomas Publisher, Springfield, Ill. 1971. Chapter 29, pp. 421-432.

9. Munichoodappa CS, Rees SB, Bradley RF, Balodimos MC, Boden G: Bragg peak proton beam irradiation of the pituitary gland for proliferative diabetic retinopathy. Ann. Int. Med. 74:491-498, 1971.

10. Boden, G.: Hormonal and metabolic disturbances during acute and subacute myocardial infarction in man. Diabetologia 7:240-247, 1971.

11. Sapir, D.G., Owen, O.E., Cheng, J.T., Ginsberg, R., Boden, G. and Walker, W.G.: The effect of carbohydrates on ammonium and ketoacid excretion during starvation. J. Clin. Invest. 51:2093-2102, 1972

12. Boden, G., Lundy, L.E. and Owen, O.E.: Influence of levodopa on serum levels of anterior pituitary hormones in man. Neuroendocrinology 10:309-315, 1972.

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13. Boden, G. and Chey, W.Y.: Preparation and specificity of antiserum to synthetic secretin and its use in a radioimmunoassay (RIA). Endocrinology 92:1617, 1973.

14. Boden, G., Dinoso, V. and Owen, O.E.: Immunological comparison of natural and synthetic secretins. Horm. Metab. Res. 1973. In press.

15. Rogers, P., Boden, G. and Tourtelotte, C.: Relapsing polychondritis with insulin resistance and anticartillage antibodies. Amer. J. Med. 1973. In press.

16. Koncz, L., Soeldner, J.S., Balodimos, M.C., Boden, G., Gleason, R.E. and Younger, D.: Human growth hormone secretion after double stimulation with arginine in normal and insulin dependent diabetic women. Diabetes. 1973. In press.

17. Owen, O.E., Reichard, G.A., Jr., Boden, G., and Shuman, C.: Comparative measurements of glucose, beta-hydroxybutyrate, acetoacetate and insulin in blood and cerebrospinal fluid during starvation. Metabolism. 1973. In press.

18. Owen, O.E., Reichard, G.A., Jr., Markus, H., Boden, G., Mozzoli, M. and Shuman, C.R.: Rapid intravenous sodium acetoacetate infusion in man: Metabolic and kinetic responses. J. Clin. Invest. 1973, In press.

19. Boden, G.: The secretin radioimmunoassay. In Methods of Hormone Radioimmunoassay. B.M. Jaffe and H. Behrman, eds. Academic Press. 1974, In press. Chapter 27.

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# CURRICULUM VITAE

Name: REDACTED

Date of Birth: REDACTED

Immigration Status: REDACTED

Marital Status: REDACTED

Educational Qualifications:

1. B. Sc. University of Mysore, India. May, 1964.

2. B. Pharm. Bangalore University, India. June, 1968.

3. Ph.D. Natural Product Chemistry. Philadelphia College of Pharmacy and Science. Philadelphia, May, 1973.

Professional Experience:

1. Graduate Assistant (1968-1973). Philadelphia College of Pharmacy and Science.

Publications:

1. Murthy, S.N.S. and A.D. Marderosian: Isolation and identification of the toxic saponin principles from sea cucumbers. Proc. 3rd Food and Drugs from Sea Conference. Rhode Island, 1973 (in press).

2. Murthy, S.N.S. and A.D. Marderosian: The isolation and identification of Rodiasine from Ocotea venenosa. Lloydia. 1973 (in press).

3. Marderosian, A.D. and S.N.S. Murthy: The analysis of old samples of Canabis sativa L. Proc. Soc. Econ. Bot., 1972 (Abstract).

4. Marderosian, A.D., H. Pinkley, F. Goldstein and S.N.S. Murthy: The ethanobotany, phytochemistry and pharmacology of Amazon arrow poison used by Kofan Indians. Proc. II International Botanical Congress, San Diego, 1969. p. 72.

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